

4-Methylphenol, reaction products with dicyclopentadiene and isobutylene

Category Justification and Testing Rationale

CAS No. 68610-51-5

Rubber and Plastic Additives Panel of the
American Chemistry Council
July 2003

List of Member Companies in the Rubber and Plastic Additives Panel

The Rubber and Plastic Additives Panel of the American Chemistry Council includes the following member companies: Alco Chemical Corporation; Bayer Polymers LLC.; Ciba Specialty Chemicals Corporation; Crompton Corporation; Eliokem, Inc.; Flexsys America L.P.; The Goodyear Tire & Rubber Company; The Lubrizol Corporation; Noveon, Inc.; and R.T. Vanderbilt Company, Inc.

Executive Summary

The American Chemistry Council's Rubber and Plastic Additives Panel (RAPA) and its member companies submit this test plan for 4-methylphenol, reaction products with dicyclopentadiene and isobutylene (68610-51-5) under the Environmental Protection Agency's High Production Volume (HPV) Challenge Program. This submission for CAS number 68610-51-5 constitutes a partial revision of documents previously submitted to the Program by the RAPA Panel. In the previous submission, dated December 18, 2001, CAS number 68610-51-5 was included in a category called "Hindered Phenols." In comments dated December 5, 2002, EPA noted that *"the data provided by the sponsor support the category with respect to the physicochemical, environmental fate and ecotoxicological properties of these substances; the health endpoints are less well supported."* Comments received from Environmental Defense (dated May 23, 2002) also noted questions about the "Hindered Phenols" as a category. Accordingly, in response to these comments, revised Test Plans and Robust Summaries for the eight chemicals that comprised the former "Hindered Phenols" category will be submitted as two categories (Styrenated Phenols and Bridged Alkyl Phenols) and two stand-alone chemicals (CAS numbers 68610-51-5 and 27676-62-6).

4-Methylphenol, reaction products with dicyclopentadiene and isobutylene is an additive for natural rubber, synthetic rubber, plastics and adhesives. Its sole purpose is to prevent or greatly delay the deterioration caused by air oxidation. Usage levels for most applications are typically within the range of 1 to 5%. Due to its low toxicity and low volatility, it is approved for use by the Food and Drug Administration (FDA) in a number of food-contact applications as an Indirect Food Additive.

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In consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals, the Panel has conducted an extensive literature search for all available data, published and unpublished. It has also performed an analysis of the adequacy of the existing data. It is concluded that there are sufficient data for this substance for the purposes of the HPV Program and no additional testing is recommended.

Physiochemical Properties

4-Methylphenol, reaction products with dicyclopentadiene and isobutylene is a solid at room temperature. It has low water solubility and a high partition coefficient.

Fate and Transport Characteristics

4-Methylphenol, reaction products with dicyclopentadiene and isobutylene is not biodegradable. Because of low water solubility, hydrolysis cannot be determined. The environmental transport model was not applicable, but with low water solubility and a low vapor pressure, it would be expected that partitioning would be to soil and sediment and not air and water.

Toxicology

Aquatic Toxicology. Acute aquatic toxicity tests are available in fish, invertebrates, and algae. The substance was shown to be non-toxic to its limit of water solubility (>0.2 mg/mL) for all three species.

Mammalian Toxicology - Acute. Acute oral and dermal toxicity data are available and show that the substance is not acutely toxic.

Mammalian Toxicology - Genotoxicity. *In vitro* gene mutation assays and *in vitro* chromosome aberrations assays are available. All mutagenicity tests were negative.

Mammalian Toxicology – Repeated Dose Toxicity. A 90-day repeated oral toxicity study is available.

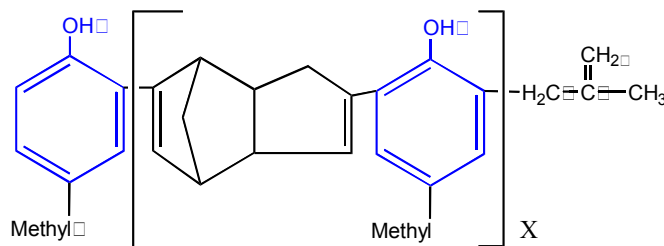
Mammalian Toxicology - Reproductive and Developmental Toxicity.

A developmental toxicity study in rats is available. The substance was not teratogenic, but did show a slight increase in the incidence of common fetal skeletal variations. Reproduction studies with 4-methylphenol, reaction products with dicyclopentadiene and isobutylene are not available, however, the 90-day repeated-dose oral toxicity study included evaluation of male and female reproductive organs. No adverse effects on reproductive organs were observed.

Conclusion.

The test plan was developed giving careful consideration to the number of animals that would be required for any tests that are not available for 4-methylphenol, reaction products with dicyclopentadiene and isobutylene. It is concluded that there are adequate data to assess the toxicity of 4-methylphenol, reaction products with dicyclopentadiene and isobutylene for the purposes of the HPV Program and no additional testing is proposed.

4-Methylphenol, reaction products with dicyclopentadiene and isobutylene (68610-51-5)



Background Information: Manufacturing and Commercial Applications

Manufacture

4-Methylphenol, reaction products with dicyclopentadiene and isobutylene is manufactured in a two-stage process. p-Cresol is reacted with dicyclopentadiene, followed by butylation. The reactions occur in an organic solvent with a catalyst. The solvent and catalyst are removed, resulting in a product that is a solid at room temperature.

Commercial Applications

4-Methylphenol, reaction products with dicyclopentadiene and isobutylene is an additive for natural rubber, synthetic rubber, plastics and adhesives. Its sole purpose is to prevent or greatly delay the deterioration caused by air oxidation. Usage levels for most applications are typically within the range of 1 to 5%.

Due to its low toxicity and low volatility, 4-methylphenol, reaction products with dicyclopentadiene and isobutylene it is approved for use by the Food and Drug Administration (FDA) in a number of food-contact applications as an Indirect Food Additive:

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|----------|--|
| 175.105 | Components of Adhesives |
| 175.125 | Pressure-Sensitive Adhesives |
| 177.2600 | Rubber Articles – Antioxidants |
| 178.2010 | Antioxidants and/or Stabilizers for Polymers (ABS copolymers only) |

Shipping/Distribution

4-Methylphenol, reaction products with dicyclopentadiene and isobutylene is manufactured in the United States and Europe and is shipped worldwide for use at manufacturing sites engaged in the production of rubber and plastic articles and food containers.

Worker/Consumer Exposure

The rubber and plastics additives industry has a long safety record and sophisticated industrial users handle this material. Exposure of workers handling 4-methylphenol, reaction products with dicyclopentadiene and isobutylene is likely to be greater in the area of material packaging rather than from chemical manufacturing. During material packaging at the manufacturing site and, to a somewhat lesser degree during weigh-up activities at the customer site, there is a potential for dermal exposure. Because of its low vapor pressure, inhalation exposure is expected to be negligible.

Sales of 4-methylphenol, reaction products with dicyclopentadiene and isobutylene are to industrial users. There are no consumer uses for this material as manufactured, so there are no known direct-to-consumer sales. Only very small amounts are used in the manufacture of rubber and plastics. Consumer exposure to 4-methylphenol, reaction products with dicyclopentadiene and isobutylene is judged to be minimal. Should exposure occur, the most likely route would be skin contact from rubber and plastic articles.

Table 1 summarizes the data available for 4-methylphenol, reaction products with dicyclopentadiene and isobutylene (CAS No. 68610-51-5).

Physicochemical Properties

The substance is a solid at room temperature with a low vapor pressure. Water solubility of 4-methylphenol, reaction products with dicyclopentadiene and isobutylene is limited and the partition coefficient is high.

Environmental Fate

Experimental data show that 4-methylphenol, reaction products with dicyclopentadiene and isobutylene is not biodegradable. Because of low water solubility, hydrolysis cannot be determined. The environmental transport model was not applicable to the substance. With low water solubility and low vapor pressure, it would be expected that partitioning would be to soil and sediment and not air and water.

Ecotoxicity

Acute aquatic toxicity tests are available in fish, invertebrates, and algae. 4-Methylphenol, reaction products with dicyclopentadiene and isobutylene has been shown to be non-toxic to its limit of water solubility (>0.2 mg/mL) in all species tested.

Toxicology

Acute toxicity: The substance has not been shown to be acutely toxic. The oral LD50 in rats is >5000 mg/kg and the dermal LD50 is >5010 mg/kg.

Genotoxicity: *In vitro* gene mutation assays are available in bacteria and cultured mammalian cells. The substance has been evaluated in cultured mammalian cells for chromosome aberrations *in vitro*. All genotoxicity tests with 4-methylphenol, reaction products with dicyclopentadiene and isobutylene were negative. Available data support the conclusion that this substance does not have potential to cause genetic damage and no additional testing is proposed.

Repeated Dose Toxicity: A 90-day feeding study in rats is available for 4-methylphenol, reaction products with dicyclopentadiene and isobutylene. Limited toxicity was observed at the higher doses. Liver weights were increased in rats of both sexes at doses of 1500 ppm and higher and adrenal weights were higher in females at 1500 ppm. Microscopic examination of tissues showed no microscopic lesion associated with the organ weight effects. The NOAEL for subchronic toxicity was established at 500 ppm (25 mg/kg/day). This study adequately evaluated the repeated dose toxicity for the substance for the purposes of the HPV Program, establishing a NOAEL and LOAEL.

Reproductive and Developmental Toxicity: A developmental toxicity study in rats is available for the substance. Maternally toxic doses were tested. The substance was not teratogenic. However, it did show a slight increase in the incidence of common fetal skeletal variations. A NOAEL for material toxicity was established at 1000 mg/kg/day and a benchmark dose (BMD) at the ED₀₅ was determined for the fetal variations at 740 mg/kg/day. The developmental toxicity study adequately evaluated the potential of 4-methylphenol, reaction products with dicyclopentadiene and isobutylene to cause developmental toxicity for the purposes of the HPV Program.

While a multigeneration reproduction study has not been conducted with 4-methylphenol, reaction products with dicyclopentadiene and isobutylene, the 90-day repeated-dose oral toxicity study included evaluation of male and female reproductive organs. No adverse effects on reproductive organs were observed grossly or microscopically.

This endpoint has been adequately evaluated for HPV purposes with the developmental toxicity study and evaluation of reproductive organs of animals of both sexes after 90 days of exposure to the substance.

Conclusion

The test plan was developed giving careful consideration to the number of animals that would be required for any tests that are not available for 4-methylphenol, reaction products with dicyclopentadiene and isobutylene (68610-51-5). The availability and adequacy of the data for the test plan are summarized in Table 1 and 2. It is concluded that there are adequate data to assess the toxicity of 4-methylphenol, reaction products with dicyclopentadiene and isobutylene for the purposes of the HPV Program and no additional testing is proposed.

Table 1.
Matrix of Available and Adequate Data for
4-Methylphenol, reaction products with dicyclopentadiene and isobutylene
(CAS No. 68610-51-5)

Physicochemical Properties	
Molecular Weight	750 – 850
Boiling Point	NA
Melting Point	118.3 °C
Vapor Pressure	< 2.4 x 10 ⁻⁷ mm Hg at 25 °C
Water Solubility	0.2 at mg/L 20 °C
Partition Coefficient	7.17 - 8.17
Environmental Fate	
Hydrolysis	cbd
Photodegradation	cbd (EPIWIN)
Biodegradation	Not biodegradable
Environmental Transport	cbd (EPIWIN)
Ecotoxicity	
Acute Fish 96-hr LC50	>0.2 mg/L (limit of solubility)
Acute Invertebrate 48-hr EC50	>0.2 mg/L (limit of solubility)
Algal Growth inhibition EC50	>0.2 mg/L (limit of solubility)
Acute Toxicity	
Oral	> 5010 mg/kg
Dermal	> 5010 mg/kg
Genotoxicity	
Bacterial Gene Mutation	negative
Mammalian Cell Gene Mutation	negative
Bacterial DNA Damage	negative
Chromosomal Aberration	
In vitro	negative
In vivo	NDA
Repeated Dose Toxicity	
Subchronic	90-Day feeding study in rats - Increased liver wt and increased adrenal wt (females only) at 1500 ppm and higher. NOAEL = 500 ppm (25 mg/kg/day)
Reproductive and Developmental Toxicity	
Reproductive	Histopathology of sex organs from 90-day repeated dose study in rats. No adverse effects.
Developmental	In rats - Not teratogenic; increased incidence of common fetal skeletal variations. NOAEL for maternal tox = 1000 mg/kg/day. BMD at ED ₀₅ for fetal variations = 740 mg/kg/day

cbd - cannot be determined due to low solubility
 cbd (EPIWIN) - cannot be determined by modeling
 NA – Not applicable
 NDA - No data available

Table 2.
Test Plan for
4-Methylphenol, reaction products with dicyclopentadiene and isobutylene
(68610-51-5)

Physicochemical Properties	
Boiling Point	NA
Melting Point	A
Vapor Pressure	A
Water Solubility	A
Partition Coefficient	A
Environmental Fate	
Hydrolysis	NA
Photodegradation	NDA
Biodegradation	A
Environmental Transport	NDA
Ecotoxicity	
Acute Fish 96-hr LC50	A
Acute Invertebrate 48-hr EC50	A
Algal Growth inhibition EC50	A
Acute Toxicity	
Oral	A
Dermal	A
Genotoxicity	
Bacterial Gene Mutation	A
Mammalian Cell Gene Mutation	A
Bacterial DNA Damage	A
Chromosomal Aberration	
In vitro	A
In vivo	NDA
Repeated Dose Toxicity	
Subchronic	A
Reproductive and Developmental Toxicity	
Reproductive	A
Developmental	A

A - Endpoint requirement fulfilled with adequate existing data

NA - Not applicable due to physical/chemical properties

NDA – No data available